Poster 1271

IDWeek 2020
www idweek org
October 21–25, 2020

Efficacy and Safety of Cefiderocol and Best Available Therapy in Patients with Serious Infections Caused by Carbapenem-Resistant Gram-Negative Pathogens: Results of the Pathogen-Focused Phase 3 CREDIBLE-CR Study

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Introduction

Infections due to carbapenem-resistant (CR) *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Escherichia coli* are considered to be a global health threat; yet treatment options are limited.[1–4]

Cefiderocol is a first-in-class siderophore cephalosporin and has potent *in vitro* activity against both CR Enterobacterales (CREs) and CR non-fermenters. Cefiderocol enters bacteria via iron-transport proteins, and it is stable against hydrolysis by all Ambler classes of carbapenemases. The activity of cefiderocol is exerted irrespective of the underlying mechanism of carbapenem resistance.[3–6]

Cefiderocol has been approved for the treatment of complicated urinary tract infections (cUTIs), and hospital-acquired and ventilator-associated bacterial pneumonia in the USA,[7] and for the treatment of infections caused by aerobic Gram-negative bacteria in adults with limited treatment options in Europe[8] under a streamlined development program.[9]

The CREDIBLE-CR study aimed to assess the efficacy and safety of cefiderocol or best available therapy (BAT) for the treatment of serious CR Gram-negative infections, regardless of species or infection-site source.[10,11]

Methods

Study design

- This was an open-label, prospective, multicenter, parallel-group, Phase 3, randomized study in patients with evidence of CR Gram-negative bacterial infections (NCT02714595).[10,11]
- Patients were randomized 2:1 to receive intravenous (IV) treatment either with cefiderocol 2 g, q8h, infused over 3 hours, for 7–14 days or BAT. BAT was pre-specified and comprised up to three systemic antibiotics, dosed according to the country's label. The duration of therapy in both arms could be extended to 21 days.[10,11]
- Patients not responding to therapy at early assessment (Day 3–4) could receive a change in antibiotic therapy (rescue therapy).
- The study was descriptive, without inferential testing.

Key inclusion and exclusion criteria

Inclusion criteria

- Hospitalized adults with HAP, VAP, healthcare-associated pneumonia (HCAP), or bloodstream infection (BSI)/sepsis, or complicated urinary tract infection (cUTI), caused by CR Gram-negative bacteria were enrolled.[10,11]
  - CR Gram-negative infection was confirmed by ≥1 of the following methods: 1) documented treatment failure on empiric therapy with culture-confirmed CR infection; 2) direct specimen rapid diagnostic test (PCR); 3) known colonization with a CR pathogen at the primary site of infection ≤72 hours prior to infection diagnosis; 4) infection with *Stenotrophomonas maltophilia*; 5) local hospital antibiogram demonstrating >90% CR rate of identified species.

Exclusion criteria

- Patients were excluded if they had:
  - received potentially effective antibiotics for the current CR infection within 72 hours prior to randomization (with a continuous duration of >24 hours for cUTI or >36 hours for other infections),
  - meningitis, osteomyelitis, endocarditis, cystic fibrosis, refractory septic shock (not responding to fluid resuscitation) or moderate/severe bronchiectasis,
  - Acute Physiology And Chronic Health Evaluation II (APACHE II) score >30.

Study outcomes

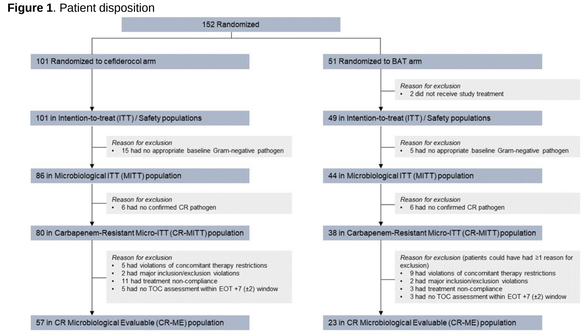
- The primary outcome at test of cure (TOC: defined as end of treatment (EOT) +7 days) was clinical cure in patients with HAP/VAP/HCAP or BSI/sepsis, and microbiological eradication in patients with cUTI, in the CR microbiological intention-to-treat (CR-MITT) population.[10,11]
- Secondary outcomes included clinical and microbiological outcomes in each indication type by patient and by pathogen at TOC, all-cause mortality (ACM) rates at Day 14 and 28. ACM at end of study (EOS) was also assessed.
- Safety was assessed throughout the study period.

Statistical analyses

- Descriptive statistics were provided for all parameters.[10,11]
- The sample size was determined by feasibility and not powered for inferential testing.
- The primary efficacy analysis population was the CR-MITT population, which included all patients with a confirmed CR pathogen at baseline receiving ≥1 dose of study medication.
- Safety analyses were performed on the safety population.

Results

Figure 1. Patient disposition



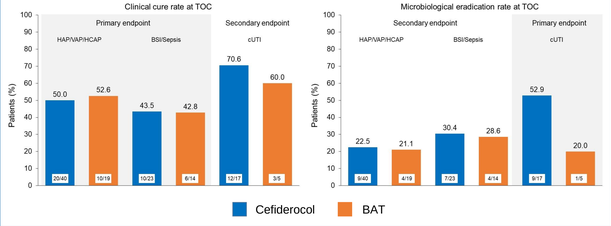
BAT, best-available therapy; CR, carbapenem resistant; EOT, end of treatment; EOS, end of study; ITT, intention to treat; CR-ME, carbapenem-resistant microbiological evaluable; CR-MITT; carbapenem-resistant microbiological intention-to-treat; MITT, microbiological intention-to-treat; TOC, Test of Cure.

Table 1. Baseline demographics and distribution of CR pathogens (CR-MITT population)

Parameter	Cefiderocol (N=80)	BAT (N=38)
Age, years		
Mean (SD)	63.1 (18.7)	62.1 (17.3)
Median (Range)	69.0 (19–92)	62.0 (19–92)
≥65 years, n (%)	50 (62.5)	17 (44.7)
Male sex, n (%)	55 (68.8)	29 (76.3)
Creatinine clearance (mL/min),		
Mean (SD)	90.30 (84.15)	98.52 (65.11)
Median (Range)	59.2 (9–540)	69.4 (5–271)
30–50 mL/min (moderate), n (%)	18 (22.5)	6 (15.8)
<30 mL/min (severe), n (%)	15 (18.8)	3 (7.9)
Clinical diagnosis at baseline, n (%)		
HAP/VAP/HCAP	40 (50.0)	19 (50.0)
BSI/sepsis	23 (28.8)	14 (36.8)
cUTI	17 (21.3)	5 (13.2)
Severity of disease, n (%)		
Moderate/Severe	76 (95.0)	35 (92.1)
Empiric treatment failure	46 (57.5)	22 (57.9)
Ventilation at randomization	44 (55.0)	23 (60.5)
ICU admission	52 (65.0)	19 (50.0)
Shock	17 (21.3)	6 (15.8)
CR Pathogens at baseline		
Acinetobacter baumannii	37 (46.3)	17 (44.7)
Klebsiella pneumoniae	27 (33.8)	12 (31.6)
Pseudomonas aeruginosa	12 (15.0)	10 (26.3)
Stenotrophomonas maltophilia	5 (6.3)	0
Acinetobacter nosocomialis	2 (2.5)	0
Enterobacter cloacae	2 (2.5)	0
Escherichia coli	2 (2.5)	1 (2.6)

ICU, intensive care unit; SD, standard deviation.

Figure 2. Outcomes at TOC (CR-MITT population). **A**. Clinical cure. **B**. microbiological eradication



Demographics and baseline characteristics

- A total of 150 patients were randomized and received treatment, of whom 118 formed the CR-MITT population (cefiderocol n=80; BAT n=38).
- Baseline demographic parameters (CR-MITT population) are shown in **Table 1**.
  - More cefiderocol- than BAT-treated patients were aged ≥65 years (62.5% and 44.7%) and had moderate or severe renal impairment (41.3% and 23.7%).
- Almost 80% of patients in each arm had one CR Gram-negative pathogen isolated at baseline, and *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* were the most frequent CR pathogens (**Table 1**).
- In the cefiderocol arm, 82.5% (66/80) of patients received cefiderocol monotherapy. In the BAT arm, a colistin-based combination regimen was given to 65.8% (25/38) of the patients. Other BAT agents included amikacin, ceftazidime-avibactam, ceftolozane-tazobactam, doripenem, fosfomycin, gentamicin, tigecycline, tobramycin or ciprofloxacin in monotherapy or combination therapy.

Table 2. Overview of treatment-emergent adverse events (safety population)

	Cefiderocol, n (%) (N=101)	BAT, n (%) (N=49)
TEAEs	92 (91.1)	47 (95.9)
Drug-related TEAEs	15 (14.9)	11 (22.4)
Discontinuation due to AEs	10 (9.9)	3 (6.1)
Discontinuation due to drug-related AEs	3 (3.0)	2 (4.1)
SAEs	50 (49.5)	23 (46.9)
Drug-related SAEs	1 (1.0)	5 (10.2)
SAEs leading to death*	34 (33.7)	9 (18.4)

SAE, serious adverse event. *Patients could have experienced ≥1 SAE that led to death.

Figure 3. Clinical and microbiological outcomes by most frequent CR pathogens at TOC (CR-MITT population)

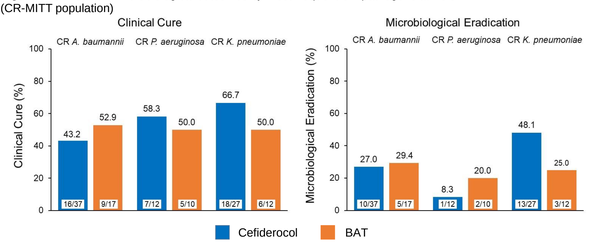


Table 3. All-cause mortality at EOS by baseline pathogen in patients with or without *Acinetobacter* spp. Infection (safety population)

Mortality by species, n/N (%)		Cefiderocol (N=101)	BAT (N=49)
All *Acinetobacter* spp.*		21/42 (50.0)	3/17 (17.6)
Acinetobacter baumannii		19/39 (48.7)	3/17 (17.6)
Klebsiella pneumoniae	with *Acinetobacter* spp.	8/34 (23.5)	4/16 (25.0)
	without *Acinetobacter* spp.	6/28 (21.4)	4/15 (26.7)
Pseudomonas aeruginosa	with *Acinetobacter* spp.	6/17 (35.3)	2/12 (16.7)
	without *Acinetobacter* spp.	2/11 (18.2)	2/11 (18.2)
Escherichia coli	with *Acinetobacter* spp.	1/6 (16.7)	0/3 (0.0)
	without *Acinetobacter* spp.	0/3 (0)	0/1 (0.0)

Table 4. Baseline clinical characteristics and mortality overall with or without *Acinetobacter* spp. infection (safety population)

	Cefiderocol (N=101)	BAT (N=49)
With *Acinetobacter* spp.*	N=42	N=17
Age ≥65 years	26 (61.9)	7 (41.2)
ICU admission	34 (81.0)	8 (47.1)
Ongoing shock	8 (19.0)	1 (5.9)
Shock <31 days prior to randomization	11 (26.2)	1 (5.9)
Mortality at EOS	**21 (50.0)**	**3 (17.6)**
Without *Acinetobacter* spp.	N=59	N=32
Age ≥65 years	38 (64.4)	15 (46.9)
ICU admission	23 (39.0)	13 (40.6)
Ongoing shock	4 (6.8)	4 (12.5)
Shock <31 days prior to randomization	8 (13.6)	5 (15.6)
Mortality at EOS	**13 (22.0)**	**6 (18.8)**

Data are n (%). ICU: intensive care unit. *Includes all carbapenem-resistant and carbapenem-susceptible of *A. baumannii* (n=39), *A. nosocomialis* (n=2) and *A. radioresistens* (n=1).

Results (continued)

Clinical and microbiological outcomes

- Clinical cure and microbiological eradication rates at TOC are shown in **Figures 2A** and **2B**, respectively.
  - For HAP/VAP/HCAP and BSI/sepsis patients, primary and secondary outcomes were similar for the cefiderocol and BAT arms.
  - For cUTI, a larger proportion of cefiderocol- than BAT-treated patients with cUTI achieved the primary outcome of microbiological eradication (52.9% and 20.0%, respectively).
  - For patients who were considered treatment failure, rescue therapy was given more frequently and from earlier time point in the BAT arm (22.4% [11/49]) than in the cefiderocol arm (12.9% [13/101]) in the ITT/Safety population.
- Clinical cure and microbiological eradication rates by most frequent CR pathogens were generally similar and are shown in **Figure 3**.
  - Clinical cure rate was 75.0% for cefiderocol and 45.4% for BAT in infections caused by metallo-beta-lactamase-producing Gram-negative pathogens, including New-Delhi metallo-beta-lactamase producing pathogens.
  - In CRE infections, the clinical cure rate was 66.7% with cefiderocol and 45.4% with BAT.

Safety

- Treatment-emergent adverse events (TEAEs) were experienced by >90% of patients in each arm (**Table 2**). Drug-related TEAEs and drug-related serious AE rates were lower in the cefiderocol arm than in the BAT arm. Discontinuations due to drug-related AEs were similar in the cefiderocol and BAT arms (3.0% and 4.1%, respectively).

Mortality

- ACM was higher for cefiderocol than BAT at Day 14 (cefiderocol: 19/101 [18.8%], BAT: 6/49 [12.2%]), Day 28 (cefiderocol: 25/101 [24.8%], BAT: 9/49 [18.4%]) and EOS (cefiderocol: 34/101 [33.7%], BAT: 9/49 [18.4%]).
  - No deaths were considered to be related to cefiderocol and one was related to BAT (ie, colistin).
  - Logistic regression analysis did not identify a single baseline parameter to be significantly associated with death.
- Mortality findings by pathogen showed an imbalance in infections caused by any *Acinetobacter* spp., but mortality rates were similar between cefiderocol- and BAT-treated patients for *P. aeruginosa* and *K. pneumoniae* infections without *Acinetobacter* spp. co-infection (**Table 3**).
  - Among patients with an *Acinetobacter* spp. infection at baseline, location at ICU at randomization, ongoing shock and shock within 31 days prior to randomization were more common in patients receiving cefiderocol compared with BAT (**Table 4**).
- Among patients without *Acinetobacter* spp. infection, mortality was similar (EOS cefiderocol 22.0% and BAT 18.8%), and 4 patients in each arm had ongoing shock in this subset (**Table 4**).

Conclusions

Imbalances in baseline characteristics were present and reflect a heterogeneous critically ill population in this relatively small study, which included multiple infection sites and in which patients were stratified only by infection diagnosis, APACHE II score and region and not by the presence of shock or ICU stay.[11]

Clinical and microbiological efficacy with cefiderocol for serious infections caused by CR pathogens, including MBL-producing pathogens, in a severely ill patient population were demonstrated.[11,12] The safety profile of cefiderocol was in general similar to that of BAT, except for rates of SAEs leading to death.[11]

A difference in mortality was observed between cefiderocol and BAT arms, but logistic regression analysis could not identify a single factor associated with higher mortality in the cefiderocol arm.[11] There was no safety signal identified than could explain the differences in mortality.

Particularly, a higher mortality was observed in patients with *Acinetobacter* spp. infections, among whom a higher proportion of patients were at the ICU and had ongoing shock at randomization or within 31 days prior to randomization which were considered to contribute to a higher risk of mortality. No mortality difference was observed in infections caused by *Pseudomonas aeruginosa* or Enterobacterales without *Acinetobacter* spp. co-infection.[11]

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